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10/623,577	07/22/2003	Raymond Pratt	109536.183	6543

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

NOTIFICATION DATE	DELIVERY MODE
12/06/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/623,577	PRATT, RAYMOND	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,37,39-43,45-52 and 54-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,37,39-43,45-52 and 54-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 36-37, 39-43, 45-52, and 54-59 are presented for examination

Applicants' amendment and Information Disclosure Statement filed 9/28/2007 have been received and entered into the application. Accordingly, claims 36, 40, 42, 46, and 48 have been amended and claims 56-59 have been added. Also, as reflected by the attached, completed copy of form 1449 the cited references have been considered.

Applicants' arguments, filed 9/28/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 9/28/2007 have been fully considered but they are not persuasive.

Instant claims 36-40, 42-46, and 48-54 were rejected under 35 U.S.C. 103 as being obvious over Ukai *et al.* (U.S. Patent No. 6,576,677).

Firstly, Applicants assert that Ukai's Test 2 teaches away from the claimed invention because a solution comprising 2% polyvinylpyrrolidone (average molecular weight 40,000) and 5 mg donepezil hydrochloride per 5 g of solution "performed poorly" in reducing bitterness. However, while it is true that this particular solution was not optimal, this does not teach away from a solution of, for example, 2% polyvinylpyrrolidone having an average molecular weight of

100,000, which is clearly encompassed by the instant claims. More importantly, the "Control" solution used by Ukai had 3 g of sorbitol per 5 g of solution, whereas the Test solutions did not. As such, one cannot determine whether 2% polyvinylpyrrolidone having an average molecular weight of 40,000 reduced bitterness compared to a solution of donepezil without sorbitol present. Further, the Ukai *et al.* patent specifically claims compositions comprising donepezil hydrochloride and 5 to 200 parts by weight of polyvinylpyrrolidone per 1 part by weight of the medicament (*e.g.*, claim 1). Dependent claims in the Ukai *et al.* patent recite further addition of propylene glycol and/or sorbitol (*e.g.*, claim 4) and an antioxidant (*e.g.*, citric acid) (claim 6). Examples provided in the Ukai *et al.* patent disclose compositions comprising donepezil HCl, polyvinylpyrrolidone, 70% D-sorbitol, citric acid, sodium citrate, sodium benzoate, flavoring agents, sodium bisulfite, propylene glycol, methylparaben, and benzoic acid in varying amounts and combinations. Accordingly, it is well within the level of ordinary skill in the art to optimize the amounts of the excipients disclosed in Ukai *et al.* in order to formulate compositions with reduced bitterness and reduced formation of analogues. Given the varying amounts of the claimed excipients taught in Ukai *et al.*, as well as the express suggestion that the amounts may be modified, the skilled artisan would appreciate that the invention of Ukai *et al.* is not limited to specific formulations. Rather, the invention is based on the discovery that compositions of donepezil HCl formulated with polyvinylpyrrolidone "reduces an unpleasant taste" (col. 2, lines 20-21). D-sorbitol and/or propylene glycol are taught to suppress the formation of analogues caused by the addition of polyvinylpyrrolidone (col. 3, lines 28-45). Thus, there is clear motivation to formulate the instantly claimed compositions.

Secondly, with respect to claims 36-40, 42-46, and 48-54, Applicants argue that Ukai *et al.* teach that polyvinylpyrrolidone can have an average molecular weight of 10,000 to 200,000 (col. 2, lines 27-37). As such, Applicants assert that the upper limit of the average molecular weight of polyvinylpyrrolidone instantly claimed is "50% less than the upper limit of the average molecular weight of the polyvinylpyrrolidone described in Ukai" (see Response, page 6). However, the instant claims recite an average molecular weight of "about 10,000 to about 100,000". Nowhere in the present application have Applicants defined to what extent "about" modifies the claimed range. As such, the average molecular weight (about 10,000 to 200,000) disclosed in Ukai *et al.* clearly obviates the claimed average molecular weights. The fact that Ukai *et al.* exemplify the use of polyvinylpyrrolidone having an average molecular weight of 40,000 (see Examples at columns 4-8) does not teach away from using polyvinylpyrrolidone having lower or higher average molecular weights because Ukai *et al.* specifically contemplate the use of a broad range of average molecular weight polyvinylpyrrolidone. Further, Ukai *et al.* teach that the larger the molecular weight of polyvinylpyrrolidone, the less the amount of it to be added. As such, there is nothing unobvious about using higher molecular weight polyvinylpyrrolidone (*e.g.*, "about 100,000") in lower amounts (*e.g.*, 0.5 to 2% by weight) as encompassed by the instant claims.

Thirdly, Applicants argue that optimization of the compositions disclosed in Ukai would require increased amounts of polyvinylpyrrolidone rather than the lower amounts required by the [instant] claims. This is not persuasive because one could also optimize the Ukai *et al.* compositions by using lower or higher molecular weight polyvinylpyrrolidone in lower or higher amounts or by adding sorbitol (e.g., Table 4). The fact that increasing the amount of

polyvinylpyrrolidone having an average molecular weight of 40,000 heightens the masking effects does not suggest that 2% polyvinylpyrrolidone having an average molecular weight of 10,000 or 0.5% polyvinylpyrrolidone having an average molecular weight of 100,000 will not mask the unpleasant taste of donepezil solutions.

Fourthly, Applicants argue that Ukai does not provide any relationship between the average molecular weight of polyvinylpyrrolidone and the amount used in the formulation. The Examiner respectfully submits that is simply not the case. While the examples is Ukai are limited to polyvinylpyrrolidone having an average molecular weight of 40,000, Ukai teaches and suggests that that polyvinylpyrrolidone having an average molecular weight of 10,000 to 200,000 is preferable (col. 2, lines 30-32) and that the ratio of basic medicament (*e.g.*, donepezil hydrochloride) to polyvinylpyrrolidone differs depending on the molecular weight and "cannot be determined in the wholesale manner" (col. 2, lines 48-51). Ukai *et al.* also teach that when larger molecular weight polyvinylpyrrolidone is used, less needs to be added, while the smaller, the more the amount to be added (col. 2, lines 60-62).

Finally, Applicants argue that the present invention is based on the "unexpected discovery" that an acceptable reduction in bitterness and numbness may be achieved even when less (*i.e.*, <2%) of such low molecular weight (*i.e.*, 40,000) polyvinylpyrrolidone is employed. However, the Examiner cannot accept this assertion of an "unexpected discovery" without evidence of such, especially in light of the fact that Applicants argue that Ukai's Test 2 (2% polyvinylpyrrolidone having an average molecular weight of 40,000) "performed poorly in reducing bitterness" (see Response, page 5). With respect to claims 40, 46, and 56-59, which recite polyvinylpyrrolidone having an average molecular weight of 40,000, Ukai *et al.* teach a

solution comprising donepezil hydrochloride and 2% polyvinylpyrrolidone having an average molecular weight of 40,000 (Test 2, Solution 4 at col. 4, lines 54-60).

It is the Examiner's position that Ukai *et al.* clearly and unequivocally suggest and motivate compositions comprising the excipients instantly claimed and Applicants have presented no evidence that the compositions instantly claimed are patentably distinct from the compositions suggested and motivated by Ukai *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 36, 37, 39-40, 42, 43, 45-46, 48-52, 54, and 56-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ukai *et al.* (U.S. Patent No. 6,576,677; Issued June 10, 2003) (prior art of record).

Ukai *et al.* disclose liquid dosage formulations of donepezil hydrochloride comprising polyvinylpyrrolidone, 70% sorbitol, a pH-adjusting agents, preservatives, solvents, antioxidants, and flavoring agents (see especially cols. 6-8). It is further disclosed that the pH of the liquid formulations is usually 3 to 7 (col. 3, lines 8-9) and can be adjusted by addition of varying amounts of citric acid, thereby teaching the pH limitations of claims 36, 39, 42, 45, 48 and 54. The reference specifically discloses orally available liquid dosage formulations comprising: (i) 5 mg donepezil HCl (0.1% by weight); (ii) 4.8% by weight povidone K30 (polyvinylpyrrolidone

with average M.W. of 40,000); (iii) 34% by weight 70% sorbitol; (iv) 0.2% by weight citric acid; (v) 0.1% by weight sodium benzoate; (vi) 0.02% by weight sodium bisulfite; and (vii) 0.3% by weight flavoring agent (col. 6, Table 4). The formulation disclosed in Table 4 does not contain a solvent (*e.g.* propylene glycol). However, an alternate formulation disclosed in the reference comprises: (i) 0.1 % by weight donepezil HCl; (ii) 5.7 % by weight povidone K30; (iii) 41% by weight 70% sorbitol; (iv) 0.2% by weight citric acid; (v) 0.1% by weight methylparaben; (vi) 6.9% by weight propylene glycol; and (vii) 0.3% by weight flavoring agent (col. 8, Example 8). The formulation disclosed in Example 8 does not contain an antioxidant. The formulations disclosed in the reference differ from the instantly claimed formulations in the amount of polyvinylpyrrolidone present in the compositions.

However, Ukai *et al.* also disclose a formulation of donepezil (5 mg), polyvinylpyrrolidone (100 mg) in a total of 5 g solution (2% polyvinylpyrrolidone) (col. 4, Test 2). It is disclosed that the formulations reduce the unpleasant taste generally associated with donepezil liquid compositions (col. 4, Table 1 and col. 5) and when an antioxidant is present in the composition (sodium bisulfite), the formulations are stable for extended periods at elevated temperatures (col. 6, lines 26-30). Further, Ukai *et al.* disclose that "the larger the molecular weight of polyvinylpyrrolidone, the less the amount of it to be added, while the smaller, the more the amount to be added" (col. 2, lines 60-62). Thus, the patent teaches that the amount of polyvinylpyrrolidone present in the formulations is highly adjustable and that the ratio of basic medicament to polyvinylpyrrolidone differs depending on the molecular weight and cannot be determined in a "wholesale manner".

In the absence of a showing of unexpected results, the present formulations would have been *prima facie* obvious given the disclosure of Ukai *et al.* Formulations comprising the instantly claimed components in amounts encompassed by the present claims are specifically disclosed in the reference. The lower amount of polyvinylpyrrolidone (0.5 to 2% and 0.1 to 3%) in the instant claims compared to the 4.8 to 5.7% in the reference formulations would have been obvious given the formulation disclosed in Test 2 (col. 4, lines 54-60) wherein only 2% polyvinylpyrrolidone and 0.1% donepezil were included in the composition. Thus, given these results and disclosure of formulations containing 2%, 4.8%, and 5.7% polyvinylpyrrolidone, and in the absence of a showing of unexpected results, no unobviousness is seen in the instantly claimed ranges of 0.5 to 2% and 0.1 to 3% polyvinylpyrrolidone. Further, Ukai *et al.* disclose that the larger the molecular weight of polyvinylpyrrolidone, the less the amount of it needs to be added, while the smaller the molecular weight, the more polyvinylpyrrolidone needs to be added (col. 2, lines 60-62). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The skilled artisan would be motivated to modify the formulation of Example 8 in the reference to include an antioxidant given the results of Test 4 (col. 6, lines 26-30) wherein a formulation containing sodium bisulfite ("Test Sample", Table 4) demonstrated better stability than a formulation wherein the antioxidant was omitted. Other antioxidants (*e.g.* sodium sulfite, ascorbic acid) are disclosed as being usable in the disclosed formulations (col. 3, line 40-45).

Accordingly, the instantly claimed formulations are deemed properly rejected as being obvious over Ukai *et al.*

Claims 41, 47, and 55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ukai *et al.* as applied to claims 36, 37, 39-40, 42, 43, 45-46, 48-52, 54, and 56-59 above, and further in view of Sugimoto *et al.* (U.S. Patent No. 4,895,841; Issued January 3, 1990) (prior art of record).

Applicant does not present any arguments specific to this rejection. Rather, Applicant argues that because the claims are unobvious over Ukai *et al.*, the claims are also unobvious over Ukai *et al.* in view of Sugimoto *et al.* The Examiner has addressed Applicant's arguments traversing the rejection of the claims over Ukai *et al.* (see *supra*). In view of the above, the present rejection is maintained for the reasons of record and reiterated below.

Sugimoto *et al.* disclose that donepezil, its hydrochloride salt, and stereoisomers (see especially col. 34, Example 4 and col. 12, lines 30-48) are capable of inhibiting acetylcholinesterase and are thus effective for the treatment of various kinds of dementia and cerebrovascular diseases (col. 29, lines 52-65). The patentees further disclose effective dosages of from generally 0.1 to 300 mg and specifically 1 to 100 mg per day (col. 30, line 25). The compounds may be orally administered (col. 30, lines 10-11) and presented in a variety of dosage forms, such as injections, suppositories, sublingual tablets, tablets, and capsules (col. 30, lines 27-31).

In the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to formulate liquid compositions comprising the enantiomers of donepezil in the formulations disclosed in Ukai *et al.* The motivation to do is found in Sugimoto who disclose that donepezil, its hydrochloride salt, and stereoisomers are

capable of inhibiting acetylcholinesterase and are thus effective for the treatment of various kinds of dementia and cerebrovascular diseases.

Accordingly, the claims are deemed properly rejected as being obvious over Ukai *et al.* in view of Sugimoto *et al.*

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

November 28, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER